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Chapter 37: Fungal Infections, Superficial

VULVOVAGINAL CANDIDIASIS

- *Vulvovaginal candidiasis* (VVC) refers to infections in individuals with or without symptoms who have positive vaginal cultures for *Candida* species. It may be sporadic or recurrent.
- Approximately 75% of women would have had at least one episode of VVC in their lifetime.
- *C. albicans* is the major pathogen responsible for VVC, accounting for 80%–90% of VVC episodes. The remainder are caused by non–*C. albicans* species, including *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*.
- Pregnancy, uncontrolled diabetes mellitus, immunosuppression, and stress are known risk factors for VVC. Frequent sexual activity and oral-genital sex can facilitate development of VVC.
- Medications known to cause alterations in vaginal microbiota and increase the risk of VVC include antibiotics (particularly broad-spectrum agents), oral contraceptives and hormone replacement therapy with high concentrations of estrogen, and sodium-glucose cotransporter-2 inhibitors.

CLINICAL PRESENTATION

- Symptoms include intense vulvar itching, soreness irritation, burning on urination, and dyspareunia.
- Signs include erythema, fissuring, curdy "cheese"-like discharge, satellite lesions, and edema.
- Laboratory tests: Vaginal pH—normal saline, and 10% potassium hydroxide (KOH) microscopy for blastospores or pseudohyphae.
- *Candida* cultures are not recommended unless classic signs and symptoms with normal vaginal pH and microscopy are inconclusive or recurrence is suspected.
- The diagnosis should be based on the presence of signs and symptoms plus a positive 10% KOH wet mount (showing yeast, hyphae, or pseudohyphae) or a positive culture that demonstrates yeast. Vaginal culture or polymerase chain reaction is recommended for definitive diagnosis in cases of complicated VVC.

TREATMENT

- Goals of Treatment: Resolve all symptoms in patients who have symptomatic VVC. No treatment is needed or recommended for asymptomatic *Candida* colonization of the vaginal mucosa.
- Patients should be counseled on adjunctive behaviors such as cleansing of the vaginal area with mild, unscented soap, wiping front to back after using the toilet, changing pads or tampons frequently during periods, and keeping the genital area dry.
- Patients should avoid prolonged hot tub use, scented tampons or hygiene products, or douching.
- Probiotics and other natural or alternative therapies are not recommended for the treatment of VVC.

Pharmacologic Therapy

- Antifungal treatment is typically required for VVC to resolve infection and prevent complications or recurrences.

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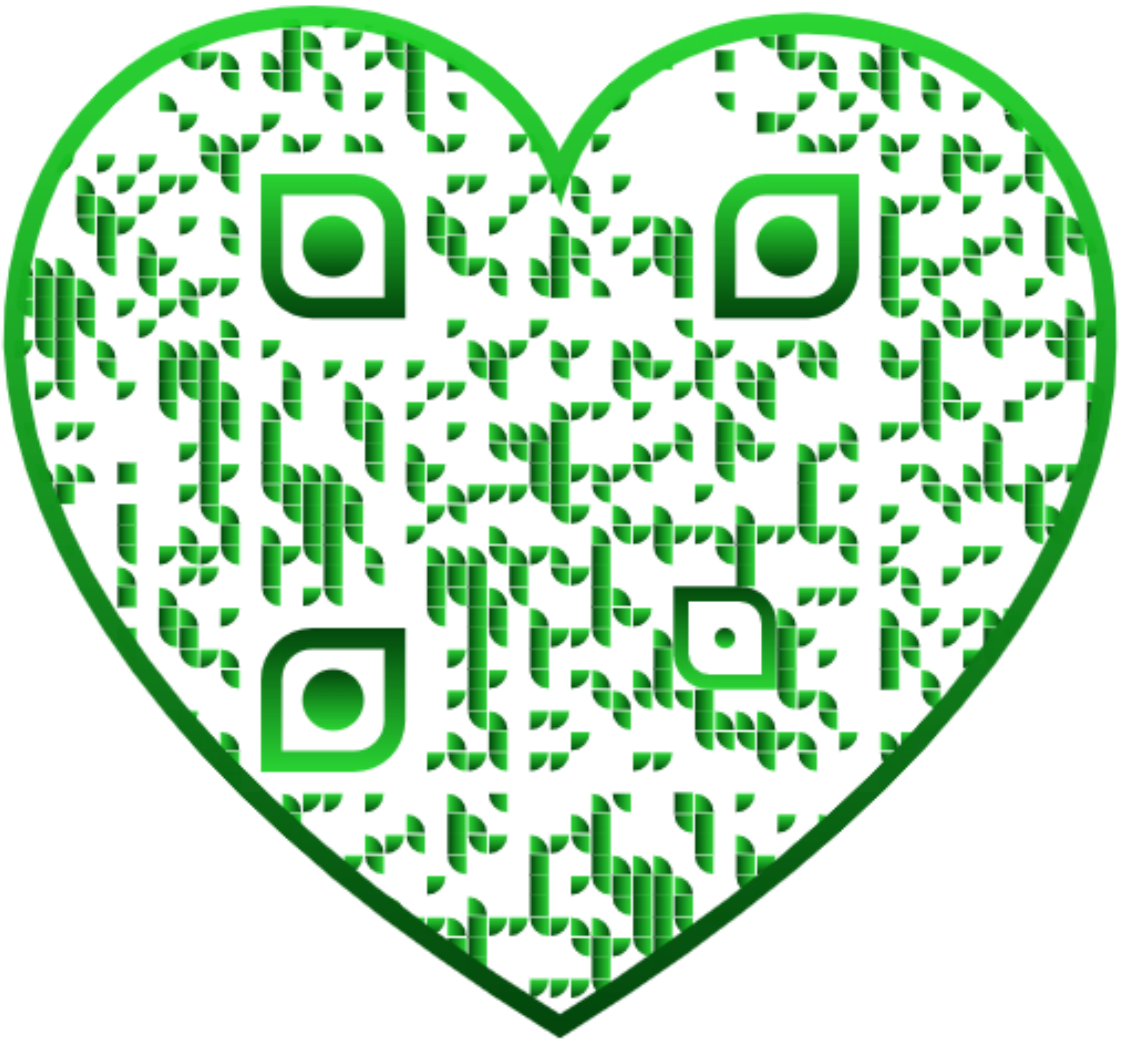

- **Table 37-1** lists treatments for uncomplicated VVC. Short-course topical or oral therapies with azole antifungals are equally effective. Topical regimens are equally recommended, and may be selected based on patient or provider preference. Oral **fluconazole** is therapeutically equivalent to topical therapies and may be preferred by some patients due to ease of administration.
- For severe infections, the Infectious Diseases Society of America (IDSA) recommends a topical agent for 5–7 days or oral fluconazole 150 mg every 72 hours for two to three doses, while the Centers for Disease Control and Prevention (CDC) recommends topical therapy for 7–14 days or oral fluconazole every 72 hours for two doses.
- Pregnant females with VVC should be treated with topical therapy for 7 days. Oral therapy is not recommended as larger doses of fluconazole have been linked to spontaneous abortion and birth defects. Oral **ibrexafungerp** and oral **oteseconazole** are contraindicated during pregnancy.
- Patients with recurrent VVC should have identification and susceptibility testing of the causative yeast and receive induction therapy with standard topical therapies or oral fluconazole with duration extended to 10–14 days. Following induction, maintenance therapy with fluconazole 150 mg weekly is recommended for 6 months.
- Women should be instructed to monitor for resolution of symptoms, which ideally occurs within 48–72 hours of treatment. If symptoms remain unresolved or recur less than 2 months later, patients should be referred to a clinician for evaluation and testing.

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TABLE 37-1

Treatment for Uncomplicated VVC

Active Ingredient	Preparation	Regimen
Nonprescription/Topical Vaginal Products		
Clotrimazole	1% cream	One applicator × 7–14 days
	2% cream	One applicator × 3 days
Miconazole[a]	2% cream	One applicator × 7 days
	4% cream	One applicator × 3 days
	100 mg suppository	One 100 mg suppository × 7 days
	200 mg suppository	One 200 mg suppository × 3 days
	1200 mg vaginal suppository	One suppository × 1 day
Tioconazole	6.5% cream	One applicator × 1 day
Prescription/Topical		
Butoconazole	2% cream	One applicator × 1 day
Terconazole	0.4% cream	One applicator × 7 days
	0.8% cream	One applicator × 3 days
	80-mg vaginal suppository	One vaginal suppository × 3 days
Prescription/Oral Products		
Fluconazole	150 mg	One tablet × 1 day
Ibrexafungerp[b]	300 mg	One tablet every 12 hours x 1 day

[a]The FDA warns of the possible increase in the anticoagulant effects of warfarin with concomitant use.

[b]Ibrexafungerp is an alternative agent that should be reserved for patients who cannot take fluconazole.

OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS

- *Oropharyngeal candidiasis* (OPC), often referred to as thrush, and esophageal candidiasis (EC) are caused by the yeast *Candida*, most often *C. albicans*.
- Factors that can lead to symptomatic OPC and EC include use of inhaled or topical corticosteroids, broad-spectrum antibiotics and

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immunosuppressive drugs, proton pump inhibitors, dentures, xerostomia, smoking, chemotherapy and radiotherapy, HIV infection, primary immunodeficiencies, and malignancies.

- Diabetes and other endocrine disorders, such as hypothyroidism, hypoparathyroidism, and hypoadrenalism, also can predispose patients to *Candida* species overgrowth.

CLINICAL PRESENTATION

- Symptoms of OPC may include pain in the mouth or while eating and swallowing, altered taste, or a burning sensation of mouth or tongue.
- Various classifications of OPC are given in **Table 37-2**. The clinical presentation of OPC and EC is presented in **Table 37-3**.
- Diagnosis is made based on examination of the oropharynx, and typical findings include white or yellow patches on the tongue, buccal mucosa, hard or soft palate, and pharyngeal areas.
- Symptoms of EC include pain when swallowing, difficulty swallowing, or pain behind the sternum. Patients can also experience other gastrointestinal-related symptoms such as abdominal pain, heartburn, nausea, vomiting, diarrhea, weight loss, and melena.
- EC can be diagnosed by clinical signs and symptoms, especially in the presence of OPC in high-risk patients. Esophageal endoscopy can confirm diagnosis with findings of white plaques or exudates, mucosal breaks, or ulcerations.

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TABLE 37-2

Clinical Classification of OPC

Types	Population at Risk	Clinical Signs and Appearance
Pseudomembranous (thrush)	Neonates, patients with HIV or cancer, the debilitated elderly, patients on broad-spectrum antibiotics or steroid inhalers, patients with dry mouth from various causes, and smokers	Classic "cottage cheese" appearance, yellowish white, soft plaques (or milk curds) overlying areas of erythema on the buccal mucosa, tongue, gums, and throat; plaques are easily removed by vigorous rubbing but can leave red or bleeding sites underneath
Erythematous (atrophic)	Patients with HIV, patients on broad-spectrum antibiotics or steroid inhalers	Painful reddened lesions throughout the oral cavity with few, if any, white plaques
Hyperplastic (candidal leukoplakia)	Smokers	Thick white and adherent keratotic plaques commonly seen on the buccal mucosa and lateral border of the tongue; can also be seen on the lips and the bottom of the mouth; plaques cannot be easily scraped off or only partially removed; this condition is distinct from oral hairy leukoplakia, and it can progress to severe dysplasia or malignancy
Angular cheilitis	Patients with HIV, denture wearers	Painful red, ulcerative, cracking, or fissuring lesion at one or both comers of the mouth because of an inflammatory reaction; usually lesions are small and rather punctate, but occasionally they can extend in a linear fashion from the angles onto the facial skin
Denture stomatitis (chronic atrophic)	Denture wearers who tend to be elderly and have poor oral hygiene	Red, flat lesions on the mucosa beneath the denture and extend right up to the denture border; more commonly located beneath a maxillary denture, although they can be encountered beneath a mandibular denture
Central papillary atrophy (median rhomboid glossitis)	Uncommon (<1% prevalence), men more commonly infected than women (3:1)	Rhomboid-shaped hypertrophic or atrophic plaque in the mid-dorsal tongue

HIV, human immunodeficiency virus.

TREATMENT

- Goals of Treatment: Clinical cure with resolution of signs and symptoms of OPC and EC is the primary treatment outcome. Secondary outcomes include the minimization of antifungal toxicities and drug–drug interactions and prevention of future recurrences.

General Approach

- Selection of antifungal agents for OPC and EC depends on the extent and severity of the disease. For mild OPC, topical therapy can be used first for most patients. Available options are **clotrimazole** troches, **miconazole** mucoadhesive tablets (MMT), and **nystatin** suspension. For moderate to severe OPC and all cases of EC, systemic therapy should be used, and the first-line option is oral fluconazole.
- Identification and modification of risk factors where possible.
- Efficacy endpoints for OPC and EC are rapid symptom relief, prevention from complications, and lack of early relapse. Symptoms typically improve

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in 48–72 hours and resolve within 7–10 days.

Pharmacologic Therapy

- For OPC, initial antifungal therapy is recommended for 7–14 days and >14 days if refractory to fluconazole. Initial treatment is recommended for 14–21 days and 21–28 days if refractory to fluconazole.
- Antifungal prescribing information for OPC and EC is found in **Table 37-4**. For all topical antifungal agents, it is important to clean the mouth prior to use.
- If a patient fails topical therapy, then fluconazole should be initiated. In cases of fluconazole-refractory disease, limited clinical trial data are available to guide comparative treatment decisions. **Itraconazole** solution and **posaconazole** tablets are preferred.
- Prophylaxis with fluconazole (targeting *Candida*) or posaconazole (targeting *Aspergillus*) is recommended in patients who are at high risk of invasive candidiasis while neutropenic, such as those with acute leukemia undergoing chemotherapy or allogeneic hematopoietic stem cell transplant recipients.

TABLE 37-3

Duration of Antifungal Therapy for Oropharyngeal and Esophageal Candidiasis

Type	Episode	Duration
OPC	Initial	7–14 days
	Fluconazole-refractory	≥14 days
EC	Initial	14–21 days
	Fluconazole-refractory	21–28 days

EC, esophageal candidiasis; OPC, oropharyngeal candidiasis.

MYCOTIC INFECTIONS OF THE SKIN, HAIR, AND NAILS

- Superficial cutaneous mycoses affect up to 20%–25% of the population globally. The usual pathogens are the dermatophytes, including *Trichophyton*, *Epidermophyton*, *Microsporum*, *Arthroderma*, *Nannizzia*, *Paraphyton*, and *Lophophyton*.
- Risk factors for the development of an infection include contact with an infected individual, secondary spread from another infected site within the same host, hot and humid environments, and footwear/clothing/headwear that impedes airflow. Comorbidities such as hyperhidrosis, diabetes mellitus, obesity, and immunosuppression are risk factors.

CLINICAL PRESENTATION

- Mycotic infections of the skin have a classic appearance that presents as scaly, red patches with a raised “worm-like” border and central clearing. Infections of the nails generally present as thickened, brittle nails.
- Diagnosis usually is based on patient history, as well as the physical examination. Diagnostic tests include direct microscopic examination of a specimen after the addition of KOH or fungal cultures. The KOH test is quick, inexpensive, and easy to perform.

TREATMENT

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- A general approach to treatment of superficial mycotic infections includes keeping the infected area dry and clean and limiting exposure to others.
- Topical agents generally are considered to be first-line therapy for most tinea infections, excluding tinea barbae, tinea capitis, onychomycosis, and severe or widespread infections. Three classes of topical antifungal therapy (allylamines, azoles, benzylamines) plus miscellaneous others are recommended.
- Treatment of mycoses of the skin, hair, and nails is given in **Table 37-4**.

TABLE 37-4

Treatment of Mycoses of the Skin, Hair, and Nails

Mycosis	Topical[a,b]	Oral Regimen[c]
Tinea barbae	Treated the same as tinea capitis (see below)	
Tinea capitis	Shampoo only in conjunction with oral therapy or for treatment of asymptomatic carriers × 1–2 weeks following diagnosis	Terbinafine tablets 62.5–250 mg/day[d] × 4–12 weeks
		Griseofulvin microsize tablet or suspension 20–25 mg/kg/day × 6–12 weeks
		Griseofulvin ultramicrosize tablet 10–15 mg/kg/day × 6–12 weeks
		Fluconazole tablet or suspension 6 mg/kg/day × 3–6 weeks
		Itraconazole capsule or solution 3–5 mg/kg/day × 2–6 weeks
Tinea corporis	Butenafine 1% cream once daily × 2 weeks	Terbinafine tablets 62.5-250 mg/day[d] × 1–2 weeks
	Ciclopirox 0.77% cream or gel twice daily × 4 weeks	Itraconazole capsule or solution 200 mg/day (adults) or 3–5 mg/kg/day (children) × 1 or more weeks
	Clotrimazole 1% cream or solution twice daily × 4 weeks	Griseofulvin microsize tablet or suspension 500–1000 mg/day (adults) or 10–20 mg/kg/day (children) × 2–4 weeks
	Econazole 1% cream daily × 2 weeks	Griseofulvin ultramicrosize tablet 375–500 mg/day (adults) or 5–15 mg/kg/day (children) × 2–4 weeks
	Ketoconazole 2% cream daily × 2 weeks	Fluconazole tablets or suspension 150–200 mg weekly (adults) or 6 mg/kg once weekly (children) × 2–4 weeks
	Luliconazole 1% cream daily × 1 week	
	Miconazole 2% cream twice daily × 4 weeks	
	Naftifine 2% cream daily × 2 weeks	
	Oxiconazole 1% cream once to twice daily × 2 weeks	

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	Sulconazole 1% cream or solution once daily × 3 weeks	
	Terbinafine 1% cream daily × 1 week	
	Tolnaftate 1% cream or solution twice daily × 4 weeks	
Tinea cruris	Butenafine 1% cream once daily × 2 weeks	Terbinafine tablets 62.5–250 mg/day[d] × 1–2 weeks
	Ciclopirox 0.77% cream twice daily × 4 weeks	Itraconazole capsule or solution 200 mg/day (adults) or 3–5 mg/kg/day (children) × 1 or more weeks
	Clotrimazole 1% cream or solution twice daily × 2 weeks	Griseofulvin microsize tablet or suspension 500–1000 mg/day (adults) or 10–20 mg/kg/day (children) × 2–4 weeks
	Econazole 1% cream daily × 2 weeks	Griseofulvin ultramicrosize tablet 375–500 mg/day (adults) or 5–15 mg/kg/day (children) × 2–4 weeks
	Ketoconazole 2% cream daily × 2 weeks	Fluconazole tablets or suspension 150–200 mg weekly (adults) or 6 mg/kg once weekly (children) × 2–4 weeks
	Luliconazole 1% cream daily × 1 week	
	Miconazole 2% cream twice daily × 2 weeks	
	Naftifine 2% cream daily × 2 weeks	
	Oxiconazole 1% cream once to twice daily × 2 weeks	
	Sulconazole 1% cream or solution once daily × 3 weeks	
	Terbinafine 1% cream daily × 1 week	
	Tolnaftate 1% cream or solution twice daily × 4 weeks	
Tinea faciei	Treated the same as tinea corporis (see above)	
Tinea incognito	Discontinue steroid therapy. Treat based on location as described in this table for other tinea infections	
Tinea manuum	Treated the same as tinea pedis (see below)[e]	
Tinea pedis	Butenafine 1% cream once daily × 4 weeks or twice daily × 1 week	Terbinafine tablets 62.5–250 mg/day[d] × 2 weeks
	Ciclopirox 0.77% cream or gel twice daily × 4 weeks	Fluconazole tablets or suspension 150 mg once per week (adults) or 6 mg/kg/week (children) × 2–6 weeks
	Clotrimazole 1% cream or solution twice daily × 4 weeks	Itraconazole capsule or solution 200 mg twice daily (adults) or 3–5 mg/kg/day (children) × 1 week
	Econazole 1% cream daily × 4 weeks	

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	Ketoconazole 2% cream daily × 6 weeks	
	Luliconazole 1% cream daily × 2 weeks	
	Miconazole 2% cream twice daily × 4 weeks	
	Naftifine 2% cream daily × 2 weeks	
	Oxiconazole 1% cream once to twice daily × 2 weeks	
	Sertaconazole 2% cream twice daily × 4 weeks	
	Sulconazole 1% cream or solution twice daily × 4 weeks	
	Terbinafine 1% cream twice daily × 1–2 weeks	
	Tolnaftate 1% cream or solution twice daily × 4 weeks	
Tinea unguium (onychomycosis)	Efinaconazole 10% topical solution once daily × 48 weeks (toenails)	Terbinafine 250 mg/day × 6 weeks (fingernail) or 12 weeks (toenail)
	Tavaborole 5% topical solution once daily × 48 weeks (toenails)	Itraconazole 200 mg once daily × 6 weeks (fingernail) or 12 weeks (toenail) OR 200 mg twice daily × 1 week/month × 2 months (fingernail) or 3 months (toenail)
	Ciclopirox 8% nail lacquer: apply solution at night for up to 48 weeks (fingernails and toenails)	Fluconazole 150–450 mg weekly for 3 months (fingernail) or 6–12 months (toenail)

[a]Other products are available, including combination products.

[b]Length of therapy depends on mycotic sensitivity and severity of infection.

[c]Only capsule formulation studied; give with food for increased absorption.

[d]Weight-based dosing: 62.5 mg for 10–20 kg; 125 mg for 20–40 kg; 250 mg for >40 kg.

[e]In cases of concomitant fingernail infection or combined infection of feet and hands, oral antifungal therapy should be preferred.

See Chapter 148, Superficial Fungal Infections, authored by Kayla R. Stover Hielscher and Mary Joyce Wingler, for a more detailed discussion of this topic.

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